Practical Vaccinology

How Biology Affects Vaccine Development

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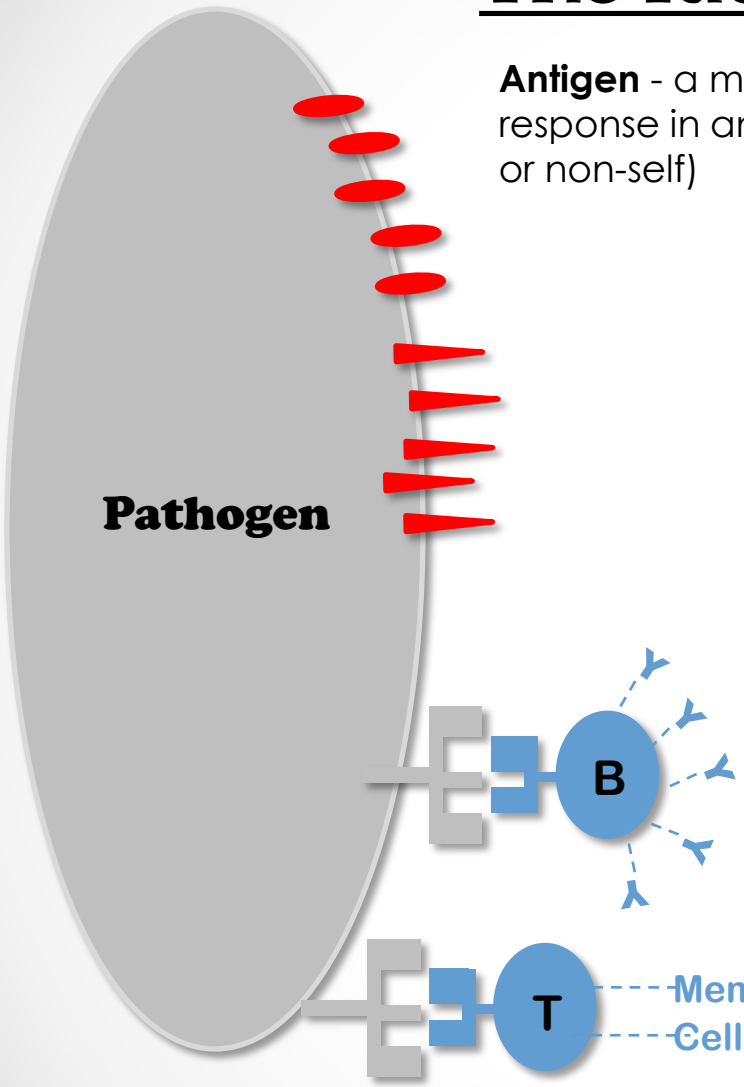
2017 Regional Immunization Workshops

Biology Lesson

- The ideal immune response
- Pathogens and their wily ways
- Types of vaccines
- Adjuvants

The Ideal Immune Response



Antigen - a molecule capable of inducing an adaptive immune response in an organism. (e.g., pathogen, toxin, poison, vaccine, self, or non-self)

Innate Immune Response

Characteristics

- General redness, swelling, pain (inflammation)
- Mucous, Pus
- Pathogen eaters (amateurs)
- Chemical announcements:
  - Invaders!
  - What type of invaders

Purpose

- Initial attack
- General
- Slow down and contain
- Call in the heavy artillery
- Direct traffic

Adaptive Immune Response

Characteristics

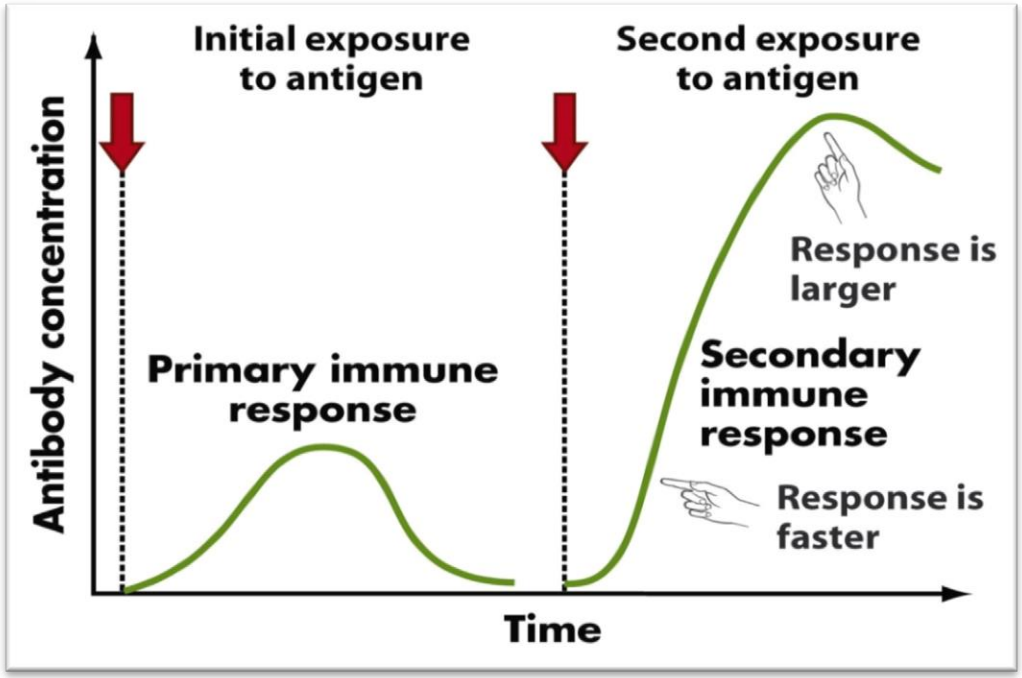
- Specific to the pathogen
- B-cells produce antibodies
- T- cells – pathogen eaters (Pros)
- T-cells – Memory, Secondary Response

Purpose

- Heavy artillery
- Inactivate the pathogen
- Recruit troops for use later
- Memory, long lasting protection

Innate Immune Response ⟷ **Adaptive Immune Response**

Adaptive Immune Response

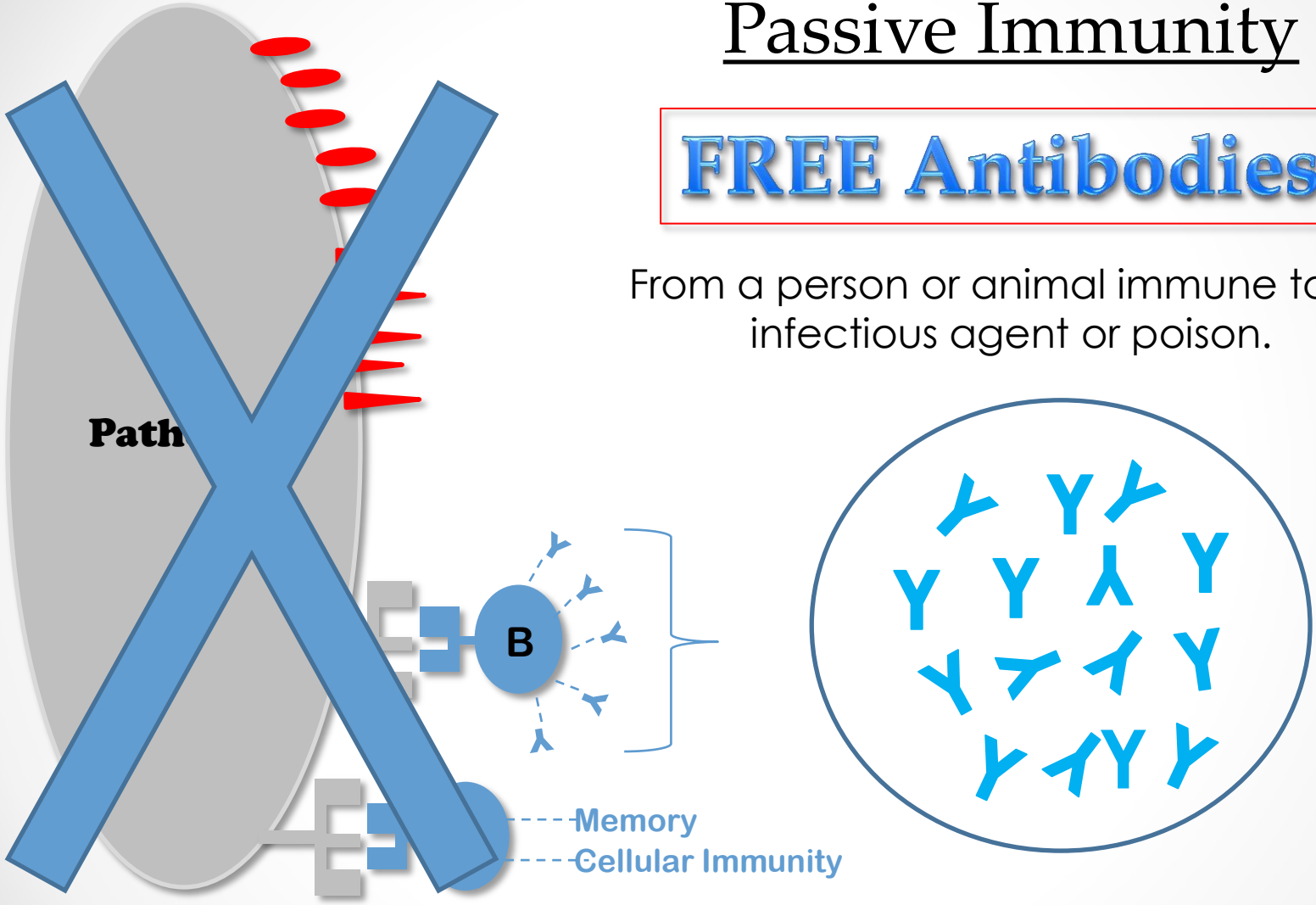


Principle of Vaccination: Trick the immune system into a primary immune response without causing disease so that the secondary immune response to the pathogen is fast, strong, and protective.

Passive Immunity

FREE Antibodies!

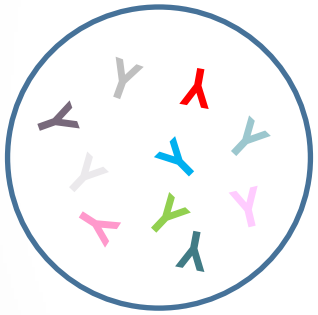
From a person or animal immune to an infectious agent or poison.



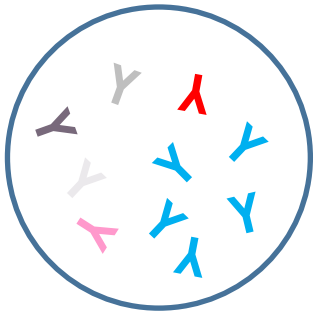
Passive Immunity

FREE Antibodies!

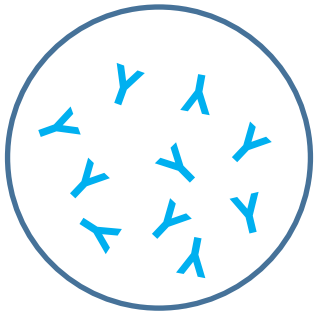
- Immediate protection
- Natural and therapeutic/prophylactic
- Homologous (human) or Heterologous (a different species)



Normal IG



Hyperimmune - HBIG



Monoclonal - Synagis

- Transient – eventually degrade
- Can be reactogenic – Foreign proteins (serum sickness)
- Can interfere with natural or vaccine-induced immune response:
  - Clears/inactivates the antigen before immune response is launched
  - Interferes with signaling and feedback mechanisms

Passive Immunity

General Rule:

Inactivated vaccines are generally not affected by circulating antibody to the antigen. Live attenuated vaccines may be affected by circulating antibody to the antigen.

Pink Book Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015.

How does this affect the live vaccine schedule?

- May delay primary series until >1 year old to avoid maternal Abs
- Co-administration of live vaccines or spaced at least 28 days apart
- Delay of vaccination after receipt of blood products that may contain antibodies to vaccine antigen

Pink Book - Appendix A-24

Recommended intervals between administration of **immune globulin preparations** and **measles-** or **varicella-containing vaccine**

Protection without Causing Harm

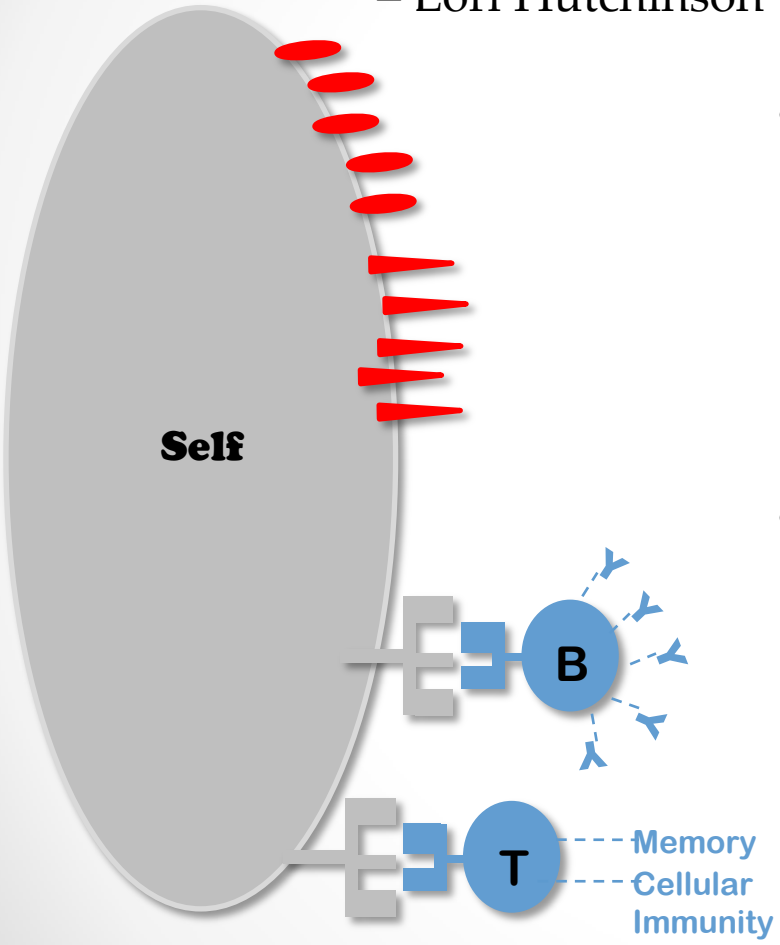
Immune responses are “expensive” and potentially harmful.

- MUST BE REGULATED.
- Lots of decisions. Lots of grey areas.
- We don’t always get it right.

	Benign	Harmful
Self	Cells of the body	Cancer cells
Non-Self	Gut bacteria Fetus	Pathogens

Immune Systems Gone Bad

"Immune systems are great until they turn on you."
– Lori Hutchinson



- **Autoinflammatory Diseases**
  (Innate Immune Response)
  - Ankylosing Spondilitis
  - Familial Mediterranean Fever
  - Bechet's Diseases

- **Autoimmune Diseases**
  (Adaptive Immune Response)
  - Multiple Sclerosis
  - Type-1 Diabetes
  - Rheumatoid Arthritis
  - Graves' Disease/Hashimoto's Thyroiditis

Pathogens and their Wily Ways

"The human immune system and the viruses hosted by our bodies are in a continual dance for survival—viruses ever seek new ways to evade detection, and our immune system devises new methods to hunt them down." --
Pamela Bjorkman, Caltech Professor of Biology

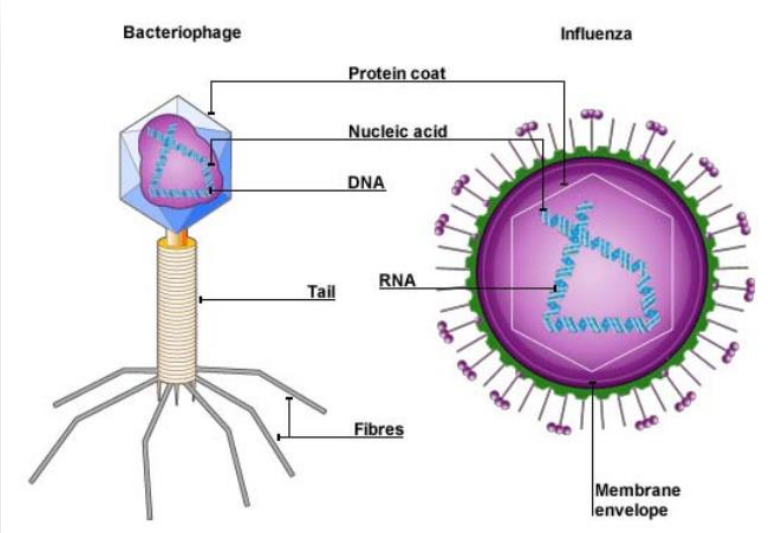
Immune System Evasion Strategies:

- Complex Structure
- Complex Virulence Strategy
- Complex Lifecycle (malaria)
- High Mutation Rate/Variability (HIV)
- Immunoevasion
  - Mimicry – Masquerading as host (bacterial polysaccharide capsules)
  - Hide – Intracellular, latency (HIV, tuberculosis, Zoster)

Human Pathogens

Viruses

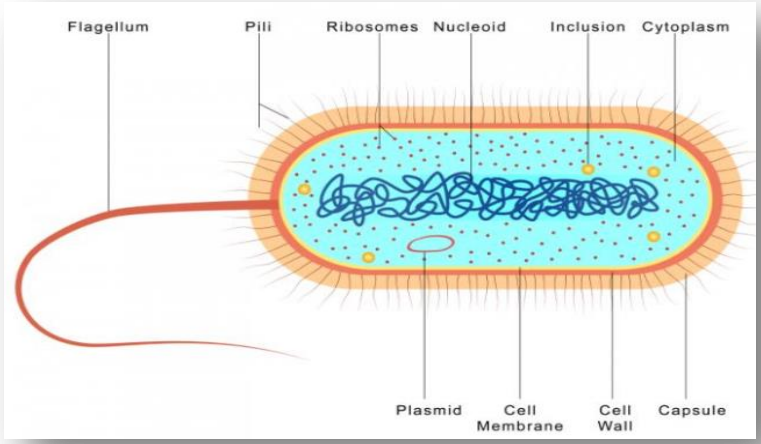
- Very small
- Simple structure - protein and either DNA/RNA
- Simple genome
- Cannot replicate on its own. Must invade and use host cells to replicate. Are they alive?
- Susceptible to antivirals NOT antibiotics



Human Pathogens

Bacteria

- Larger, more complex
- Carry out normal cell functions
- Can live and replicate on their own
- Susceptible to antibiotics



Other Nasty Bugs that are Targeted for Vaccines

- Protozoans – parasites - Malaria
- Prions – Mad Cow disease, Creutzfeldt-Jakob disease, Chronic Wasting Disease

Vaccines

Principle of Vaccination: Trick the immune system into a primary immune response without causing disease so that the secondary immune response to the pathogen is fast, strong, and protective.

Ideal Vaccine

- Full-Spectrum Immune Response
- Protective
- Safe and Low-to-non Reactive
- Economically and technologically feasible to produce
- Clear Correlate of Immunity (e.g., Ab titers)
- Can distinguish vaccine-induced versus wild-type immunity.

General Rule:

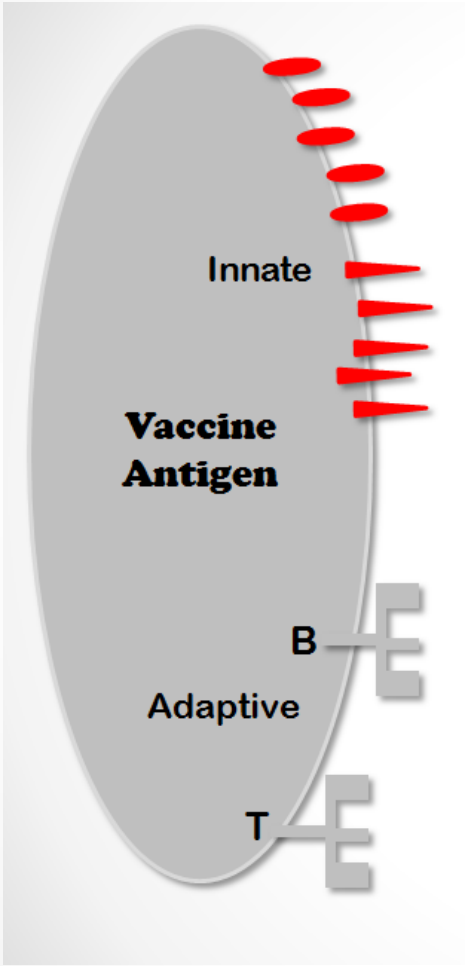
The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.

Pink Book Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015.

Common US Vaccines by Pathogen and Vaccine Type

Vaccine	Trade Name	Pathogen	Vaccine Type
MMR	MMR II, ProQuad	Virus	Whole Cell Live - Attenuated
Varicella	Varivax, Zostavax, ProQuad		
Rotavirus	RotaTeq, Rotarix		
Influenza	FluMist		
Yellow Fever	YF-Vax		
Typhoid	Vivotif	Bacteria	
Polio	IPOL, Kinrix, Quadracel, Pediarix, Pentacel	Virus	Whole Cell Killed/Inactivated
Hepatitis A	Havrix, Vaqta, Twinrix		
Rabies	Imovax, RabAvert		
Meningococcal ACWY (MCV)	Menactra, Menveo	Bacteria	Subunit – Polysaccharide Conjugate
Haemophilus influenza type b (HIB)	ActHIB, PedvaxHIB, Hiberix , Pentacel		
Pneumococcal Conjugate (PCV)	Prevnar		

Whole Cell Vaccines



Full Spectrum Immune Response

Whole Cell Vaccines

Live-Attenuated

A living version of the pathogen modified to have low or no virulence.

Methods of Attenuation

- Grow in a foreign environment:
  - Non-host species cells
  - Sub-optimal temperatures (FluMist© - cold adapted, temperature sensitive)
- Reassortment
- Splicing out virulence genes using biotechnology

- **Goal:** Change it enough so it can't cause disease but not so much that an can't replicate and disseminate.

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Rotavirus	RotaTeq, Rotarix		
Influenza	FluMist		
Yellow Fever	YF-Vax		
Typhoid	Vivotif	Bacteria	

Whole Cell Vaccines

Live-Attenuated

Advantages

- Replicates and disseminates to its target tissue.
- Full spectrum immune response
- Strong, long-lasting immunity (one dose plus one more to catch the 5% NR)
- No detailed knowledge of host-pathogen biology needed
- If it will grow in culture, it is easy to produce.

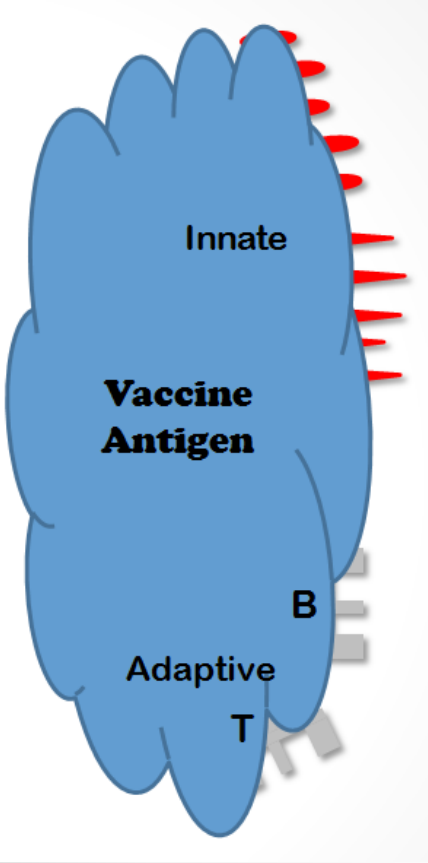
Limitations

- Contraindicated for immunocompromised people
- Local or systemic reactogenicity
- May induce mild disease (live, attenuated influenza)
- Risk of reversion (oral polio)
- Latency and immunoevasion still happen (HIV)
- Reduced immunogenicity due to over-attenuation
- Response affected by circulating antibodies
- Heat labile, susceptible to temperature excursions

Whole Cell Vaccines

Killed/Inactivated

Whole organisms that are killed or inactivated (viruses)



Methods of Killing or Inactivating

Chemical Treatment – Formalin, β-propiolactone

Polio	IPOL, Kinrix, Quadracel, Pediarix, Pentacel	Virus	Whole Cell Killed/Inactivated
Hepatitis A	Havrix, Vaqta, Twinrix		
Rabies	Imovax, RabAvert		

Whole Cell Vaccines

Killed/Inactivated

- Advantages of Whole Cell Inactivated Vaccine Approach
- "Modified" full spectrum response
- Non-infectious, no risk of reversion
- Not affected by circulating antibodies
- No detailed knowledge of host-pathogen biology needed
- If it will grow in culture, it is easy to produce.
- Can overcome latency and immunoevasion
- Relatively stable, less susceptible to temperature excursions.

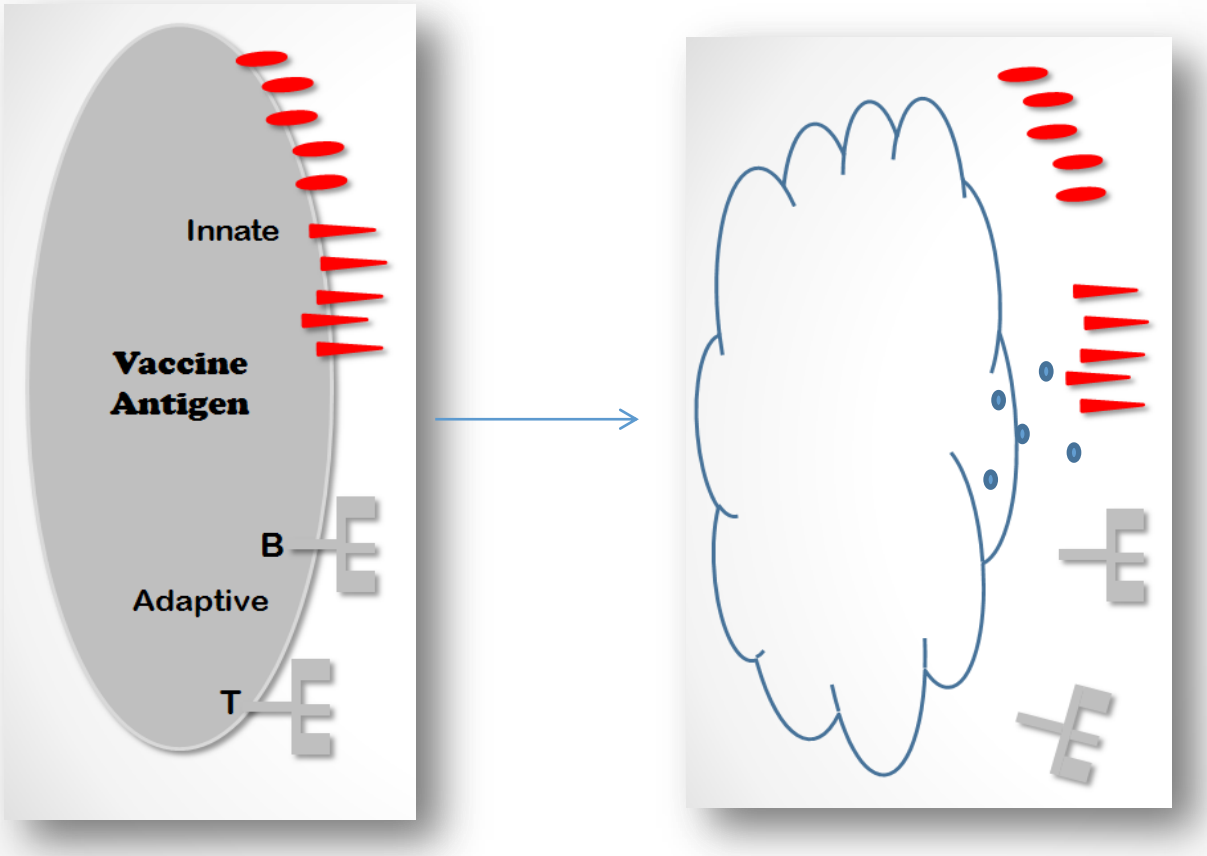
- Disadvantages of Whole Cell Inactivated Vaccine Approach
- Local or systemic reactogenicity – Whole cell Pertussis, Typhoid
- Does not replicate or migrate to host tissue
- Decreased immunogenicity
  - May need adjuvants to get a full spectrum response
  - Multiple doses needed for priming
  - May need booster doses

Common US Vaccines by Pathogen and Vaccine Type

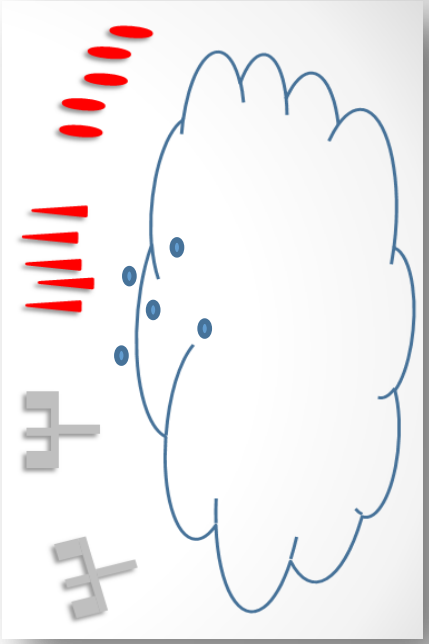
Vaccine	Trade Name	Pathogen	Vaccine Type
MMR	MMR II, ProQuad		
Tetanus	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel, Tenivac	Bacteria	Subunit - Toxoid
Diphtheria	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel		
Pertussis	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel	Bacteria	Subunit - Fractionated
Influenza	Afluria, Fluad, Fluarix, Flublok, Flucelvax, FluLaval, Fluvirin, Fluzone	Virus	
Hepatitis B	Engerix B, Recombivax HB, Pediarix	Virus	Subunit – Recombinant Protein
Human Papilloma Virus (HPV)	Gardasil 9		
Meningococcal B	Bexsero, Trumenba	Bacteria	
Pneumococcal Polysaccharide (PPSV)	Pneumovax 23	Bacteria	Subunit - Polysaccharide
Typhoid	Typhim Vi		
Meningococcal ACWY (MCV)	Menactra, Menveo	Bacteria	Subunit – Polysaccharide Conjugate
Haemophilus influenza type b (HIB)	ActHIB, PedvaxHIB, Hiberix , Pentacel		
Pneumococcal Conjugate (PCV)	Prevnar		

Subunit Vaccines

Uses pieces of the pathogen rather than the whole organism.



Subunit Vaccines



Advantages

- Low reactogenicity
- Highly focused and specific
- Non-infectious
- Synthetic production may be possible, facilitating supply
- Can overcome latency and immunoevasion issues

Disadvantages of Subunit Vaccines

- Goodbye full spectrum immune response – reduced immunogenicity
  - Multiple dose primary series and boosters needed
  - Hello, Adjuvants!
- Requires knowledge of host-pathogen biology – virulence factors
- Increased R & D time
- Can be difficult, expensive, and technology-intensive to develop and produce

Hello Adjuvants!

Adjuvant: A vaccine additive that enhances or modulates the immune response.

- Mimics missing "innate" triggers
- Makes antigen more "visible"
- Makes antigen persist longer in the tissue ("depot effect")
- Enhances communication between innate and adaptive immune response.

Benefits

- Stronger, longer-lasting immune response
- Enhanced response in low-responding populations
- Antigen sparing (pandemic situations)

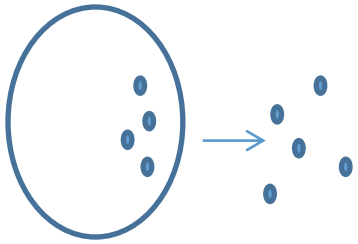
Types of Adjuvants

- Aluminum salts (most US SU vaccines)
- Liposomes (fatty containers)
- Oil/water emulsions or squalene – (FluAd©)
- Bacterial cell wall lipopolysaccharides MPL (Cervarix©)

Subunit Vaccines

Toxoids

Take advantage of a simple virulence mechanism – bacterial exotoxin



- **The Bad News about Exotoxins**
- Released from bacteria, travel to target tissue, and case damage
- Can be HIGHLY virulent

- **The Good News about Exotoxins**
- Simple molecules
- Highly immunogenic
- Easily inactivated to a "toxoid"
- Purified toxoid makes a great vaccine.

Subunit Vaccines

Toxoids

Tetanus	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel, Tenivac	Bacteria	Subunit - Toxoid
Diphtheria	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel		
Pertussis	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel	Bacteria	

All absorbed to aluminum salts as the adjuvant.

Subunit Vaccines

Fractionated

Pathogen is broken apart and pieces are isolated to use as the vaccine.

Pertussis	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel	Bacteria	Subunit - Fractionated
Influenza	Afluria, Fluad, Fluarix, Flublok, Flucelvax, FluLaval, Fluvirin, Fluzone	Virus	

Developed in response to the high reactogenicity of whole cell, inactivated vaccines.

Acellular Pertussis

- PT – Pertussis toxin
- FHA – Filamentous hemagglutinin
- PERT – Pertactin
- FIM – Fimbriae

All absorbed to aluminum salts

- Low reactogenicity
- Some studies indicate reduced immunogenicity/protection compared with whole cell vaccine.

Influenza

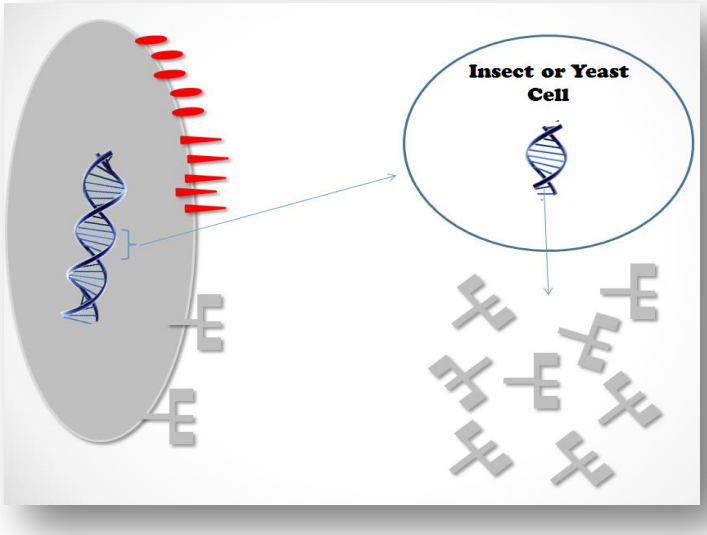
- HA - Hemagglutinin

Absorbed to aluminum salts

Subunit Vaccines

Recombinant

Genes that code for a pathogen component are inserted into another organism and the component is produced in large quantities and used as the vaccine.



- Requires intimate knowledge of host-pathogen biology
  - Structure, function, and virulence determinants
  - "gene in hand."
- Can be difficult, expensive, and technology-intensive to develop
- May be less-expensive to produce

Subunit Vaccines

Recombinant

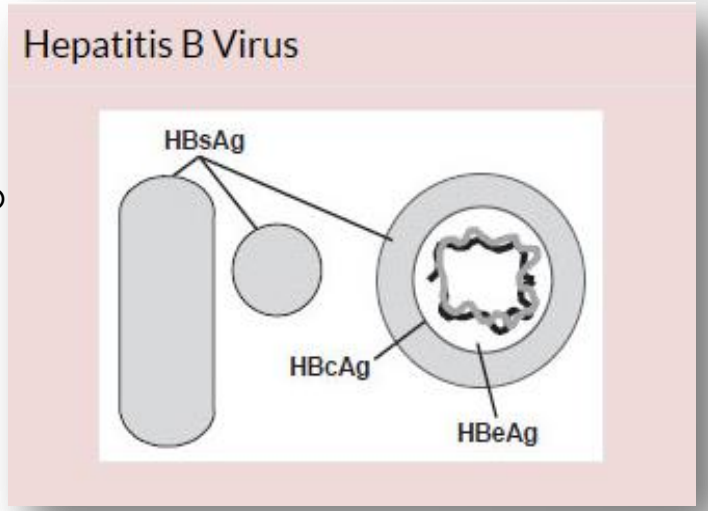
Hepatitis B	Engerix B, Recombivax HB, Pediarix	Virus	Subunit – Recombinant Protein
Human Papilloma Virus (HPV)	Gardasil 9		
Meningococcal B	Bexsero, Trumenba	Bacteria	

Subunit Vaccines

Recombinant

Hepatitis B Vaccine

- The poster child for recombinant vaccines.
- First commercial vaccine was derived from the plasma of HBV infected individuals.
- Recombinant vaccine was developed in response to safety concerns about plasma derived antigens.



Why a good candidate for a recombinant vaccine?

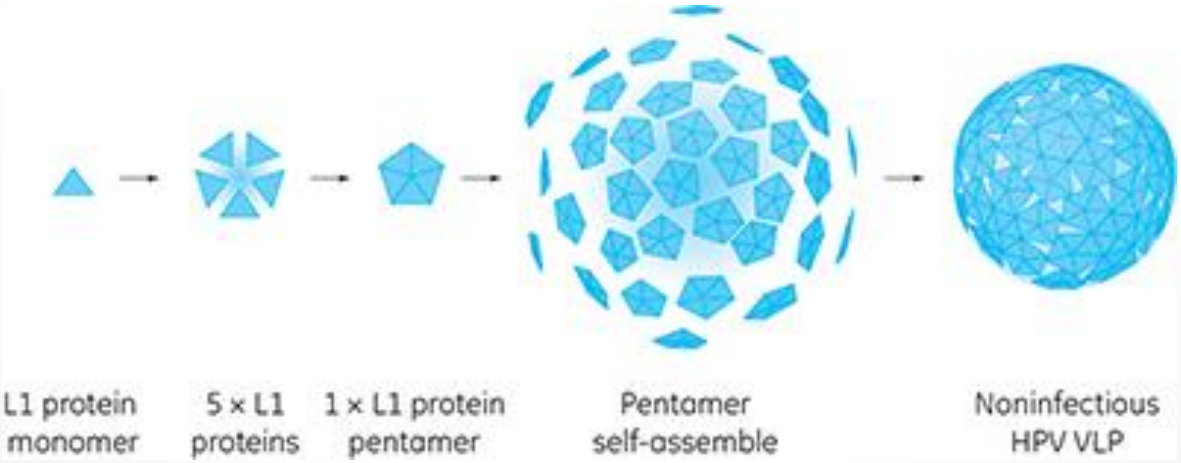
- Simple, highly conserved structure
- Hepatitis B surface antigen was an obvious virulence determinant candidate
- Easy gene to find in a simple genome
- Expressed in yeast cells, purified, and adsorbed to aluminum salts.

Subunit Vaccines

Recombinant

HPV Vaccine

- Genes for major capsid (L1) protein of nine different serotypes are expressed in yeast cells, purified, and adsorbed to aluminum salt.
- Recombinant proteins self-assemble into VLP - "virus-like particles."
- "Adjuvanted"
  - Aluminum salt (Gardasil©)
  - MPL (Cervarix©)



Subunit Vaccines

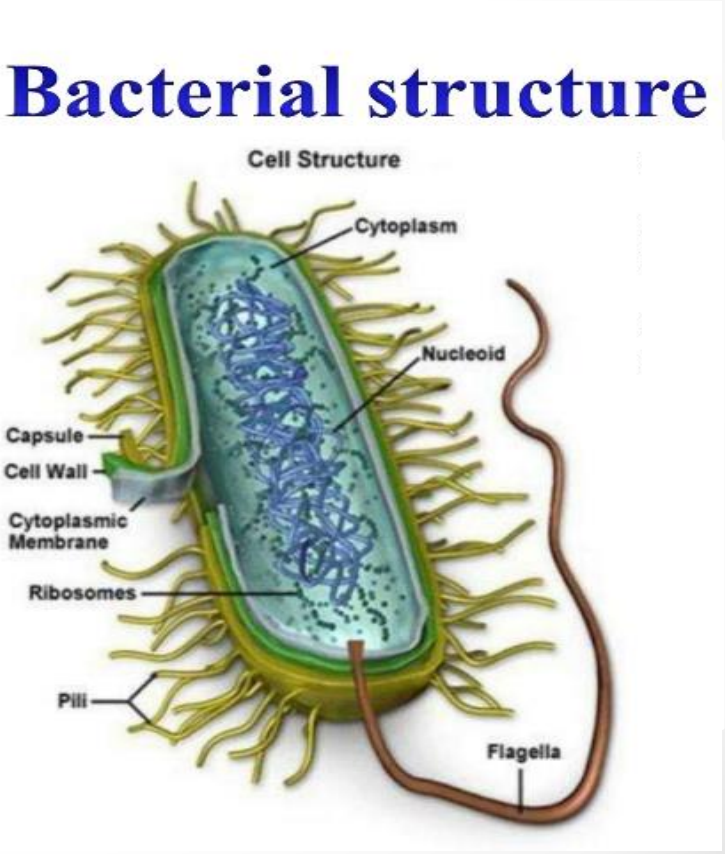
The Problem with Polysaccharides

Pathogens that cause invasive bacterial infections such as meningitis are often enclosed in a polysaccharide capsule.

Streptococcus pneumonia
Neisseria meningitides
Haemophilus influenzae

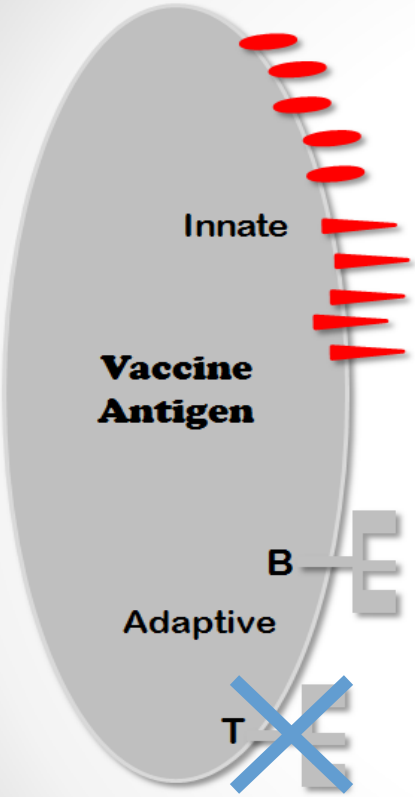
- Commensal – harmless, freeloaders until they invade the CNS meninges
- Mimicry – Invisibility Cloak

Polysaccharide



Subunit Vaccines

Pure Polysaccharides



Cell wall polysaccharides are large molecules and obvious virulence determinants.

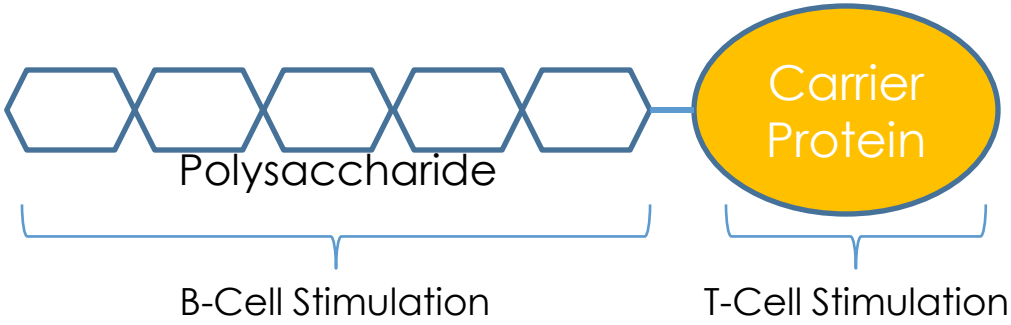
- Can be VERY immunogenic (MPL® adjuvant)
- In disease-causing bacteria, poorly immunogenic T-cell independent:
  - Age dependent response. Poorly immunogenic in children under 2 years
  - No antibody "boost" with repeated doses (no memory)

Pneumococcal Polysaccharide (PPSV)	Pneumovax 23	Bacteria	Subunit - Polysaccharide
Typhoid	Typhim Vi		

Subunit Vaccines

Polysaccharide Conjugates

Capsular polysaccharides are linked to carrier proteins known to be very immunogenic.

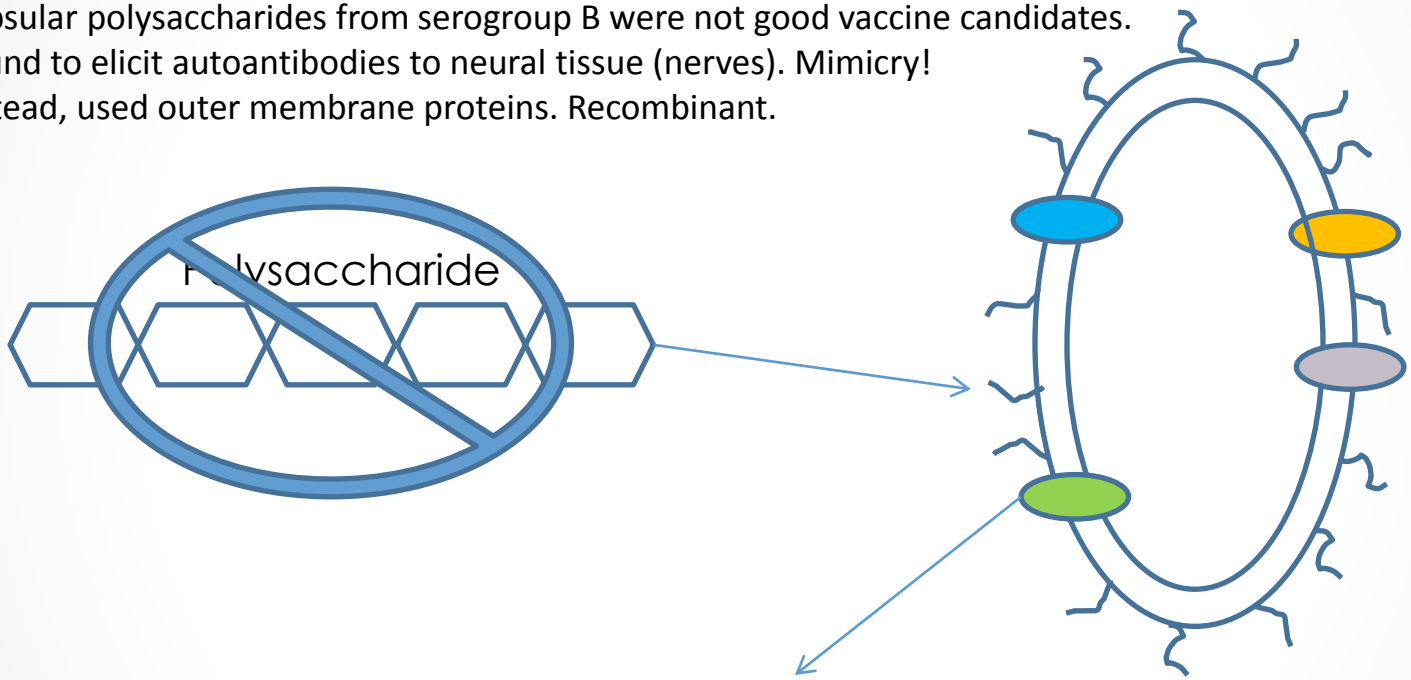


Pathogen	Vaccine	Carrier
Streptococcus pneumonia	Prevnar13	Diphtheria toxoid CRM_{197}
Neisseria meningitides (A, C, Y, W135)	Menactra	Diphtheria toxoid
	Menveo	Diphtheria toxoid CRM_{197}
Haemophilus influenzae	ActHib	Tetanus toxoid
	Hiberix	Tetanus toxoid
	Pentacel	Tetanus toxoid
	MenHibrix	Tetanus toxoid
	PedvaxHIB	OMP – outer membrane protein of *Neisseria meningitides B*
	Comvax	OMP – outer membrane protein of *Neisseria meningitides B*

Subunit Vaccines

Meningococcal B – Recombinant Protein

Capsular polysaccharides from serogroup B were not good vaccine candidates. Found to elicit autoantibodies to neural tissue (nerves). Mimicry!
Instead, used outer membrane proteins. Recombinant.



Pathogen	Vaccine	Recombinant Proteins
Neisseria meningitides (B)	Trumenba	NadA, NHBA, fHbp, OMV
	Bexsero	Two fHbp variants

Common US Vaccines by Pathogen and Vaccine Type

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MMR	MMR II, ProQuad	Virus	Whole Cell Live - Attenuated
Varicella	Varivax, Zostavax, ProQuad		
Rotavirus	RotaTeq, Rotarix		
Influenza	FluMist		
Yellow Fever	YF-Vax		
Typhoid	Vivotif	Bacteria	
Polio	IPOL, Kinrix, Quadracel, Pediarix, Pentacel	Virus	Whole Cell Killed/Inactivated
Hepatitis A	Havrix, Vaqta, Twinrix		
Rabies	Imovax, RabAvert		
Tetanus	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel, Tenivac	Bacteria	Subunit - Toxoid
Diphtheria	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel		
Pertussis	Infanrix, Daptacel, Kinrix, Quadracel, Pediarix, Pentacel	Bacteria	Subunit - Fractionated
Influenza	Afluria, Fluad, Fluarix, Flublok, Flucelvax, FluLaval, Fluvirin, Fluzone	Virus	
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Pneumococcal Polysaccharide (PPSV)	Pneumovax 23	Bacteria	Subunit - Polysaccharide
Typhoid	Typhim Vi		
Meningococcal ACWY (MCV)	Menactra, Menveo	Bacteria	Subunit – Polysaccharide Conjugate
Haemophilus influenza type b (HIB)	ActHIB, PedvaxHIB, Hiberix , Pentacel		
Pneumococcal Conjugate (PCV)	Prevnar		

Resources

- Prescribing Information (Package Insert)
  Section 11

- Stern, P; Garcon, N (Editor); Cunningham, T (Editor); Stanberry, L (Editor) /
  Understanding modern vaccines.
  http://www.sciencedirect.com/science/journal/22107622.

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